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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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The Law Offices of Valerie E. Looper
77126 Lightfall Court
Columbia, MD 21044

EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/863,606	LISZIEWICZ ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2005 and 05 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-30 and 32* is/are pending in the application.

4a) Of the above claim(s) *32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1-5-06 has been entered.

The after final amendment filed 12-23-05 has been entered. An advisory action is moot because applicants filed an RCE on 1-5-06.

Applicant's arguments filed 12-23-05 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-27 and 31 have been cancelled. Claims 28-30 and 32 remain pending.

Election/Restrictions

Claim 32 comprises an invention (Group III, administering an antiretroviral drug therapy comprising an RT inhibitor, a protease inhibitor, and hydroxyurea unit viral replication is effectively suppressed, and then administering a gene delivery complex comprising foreign genetic material and a non-viral vector, wherein the complex has a specific affinity for a receptor on an APC) nonelected with traverse in the paper filed 5-

12-03. A complete reply to the final rejection must include cancellation of the nonelected claim or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim 32 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 28-30 are under consideration in the instant application only as they relate to administering antiretroviral drug therapy comprising ddI (an RT inhibitor) and indinavir (a protease inhibitor) until viral replication is suppressed, and then administering DNA encoding an immunogenic retroviral protein operably linked with a promoter.

Specification

The amendments to the paragraphs bridging pg 22-23 and pg 23-24 have been entered and are based on the version of the paragraph filed 3-11-04.

The rejection regarding the new matter in the amendment filed 3-11-04 has been withdrawn in view of the amendment filed 12-23-05.

It is noted that MPEP 608.01 (v) states that where the identification of a trademark is introduced by amendment, it must be restricted to the characteristics of the product known at the time the application was filed to avid any question of new matter.

Claim Rejections - 35 USC § 112

New Matter

The rejection of claims 28-30 under 35 U.S.C. 112, first paragraph, new matter has been withdrawn as follows:

The rejection regarding the phrase "at least one immunogenic retroviral protein" in claim 28 has been withdrawn because pg 16, lines 15-16, contemplates using genetic material expression one or more immunogenic proteins.

The rejection regarding the limitation of "BMS 23632" in claim 30 has been withdrawn because the phrase has been deleted.

Claims 28-30 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 28-30 encompass administering antiretroviral therapy and a gene delivery complex to any host. The phase "host infected with a retrovirus" encompasses a single cellular host infected with a retrovirus, which is not supported by the specification as originally filed.

Enablement

Claims 28-30 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record.

Breadth of claims

Claims 28-30 require treating a retroviral infection in a host that is infected with a retrovirus by administering ddI and indinavir followed by DNA encoding an immunogenic retroviral protein. Administering an antiretroviral drug therapy comprising ddI and Indinavir until retroviral replication is effectively suppressed is considered enabled because Finzi taught administering a reverse transcriptase inhibitor and a protease inhibitor suppressed retroviral replication (Finzi of record. Science. Nov. 14, 1997, Vol. 278, pg 1295-1300).

Administering antiretroviral therapy comprising ddI and Indinavir as claimed does not correlate to HAART therapy. Celentano (AIDS, 2001, Vol. 15, pg 1707-1715) taught "Using IAS-USA guidelines, HAART was defined *a priori* as one of the following regimens [7,10,11]: two nucleoside reverse transcriptase inhibitors (NRTI) + PI; two PIs; two NRTIs + NNRTI; or PI + NRTI + NNRTI. Non-HAART regimens were defined as: dual NRTI, any other two-drug combination (PI+ NRTI or NNRTI + NRTI), or monotherapy" (pg 1708, col. 2, "Outcome variables"). Accordingly, claim 28 does not encompass HAART because it is a PI + NRTI.

Carpenter (JAMA, 1998, Vol. 280, No. 1, pg 78-86) is reference 10 cited by Celentano, which teach various combinations of highly active antiretroviral therapy drugs.

Kaufmann (AIDS, 2000, Vol. 14, pg 959-969) also cited Carpenter as teaching HAART as the standard care for HIV-infected subjects (pg 959, first sentence of article, reference 1).

Each limitation must be fully enabled for their disclosed use. The sole disclosed purpose for administering DNA encoding an immunogenic retroviral protein after antiviral drug therapy is to induce an immune response against the retroviral protein that is therapeutic (pg 2, lines 14-19). Therefore, the step of administering DNA encoding an immunogenic retroviral protein must be fully enabled for using the DNA to obtain a therapeutic immune response against the "immunogenic retroviral protein". As will be discussed below, the specification fails to enable those of skill to use ddI and indinavir followed by DNA encoding an immunogenic retroviral protein, so that a therapeutic immune response against the retroviral proteins encoded by the DNA is obtained.

State of the art and unpredictability of using gene delivery to treat disease

The state of the art at the time of filing was that the combination of vector, promoter, route of administration, level of expression and target tissue required to obtain a therapeutic or prophylactic effect using gene therapy was unpredictable. Miller of record (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (pg 198, col. 1). Deonarain of record (1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (pg 53, 1st ¶).

Deonarain reviews new techniques under experimentation in the art that show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma of record (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal of record (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates, "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

State of the art and unpredictability of inducing an immune response capable of treating retroviral infection

The state of the art regarding treating retroviral infection was unpredictable. Stricker of record (Medical Hypotheses, June 1997, Vol. 48, pages 527-9) teaches that attempts to develop a vaccine against HIV have been unsuccessful because HIV vaccines do not neutralize HIV (pg 527, last paragraph through all of pg 528). Overall, a lack of understanding about protective immunity to HIV in humans, the sequence variability of HIV and the rapid replication of HIV contribute the ineffectiveness of

vaccines against HIV (Bangham of record, Nov. 29, 1997, Lancet, Vol. 350, pages 1617-1621; page 1617, top of col. 1).

More specifically, Veljkovic (Vaccine, 2001, Vol. 19, pg 1855-1862) taught:

> "As was recently reported, the rgp120 subunit vaccine tested in HIV-negative individuals was not only not effective — participants in Phase I:II clinical vaccine trials who have become infected during or following immunization with the HIV-1 env had in their sera significant neutralizing antibody titers against vaccine isolates before they became infected [2,3] — but could also be dangerous [4]." (pg 1856, col. 1, first sentence of the second full paragraph)

Thus, the immune response against an HIV gp120 vaccine is inadequate to provide a prophylactic or therapeutic effect against HIV infection.

In fact, Veljkovic taught HIV can escape from immune control by HIV-specific CTL recognizing a single epitope undergoes viral mutation and is favored when the CTL response is against one HIV epitope (pg 1857, col. 1, last sentence of the first full paragraph). This phenomenon is explicitly described by McMichael (Annual Rev. Immunol., 1997, Vol. 15, pg 27-296; see entire article).

Finally, Weber (Eur. J. Clin. Microbiol. Infect. Dis., Nov. 2001, Vol. 20, pg 800-803) described the phase I clinical trial using plasmid encoding HIV-1 gp160 to treat HIV-infected humans. "Even though both trials were designed as phase I clinical trials, with special focus on safety, preliminary data suggest that vaccination with the present HIV-1 DNA construct did not show any virological or immunological efficacy, which is in contrast to findings in the chimpanzee model" (pg 802, col. 2, first sentence of first full paragraph). Thus, plasmid DNA encoding gp160 does not have a therapeutic effect in humans and using DNA encoding HIV proteins in primate models does not correlate to expected results in humans.

Teachings in the specification

The specification states:

> "The comparison of the rate of viral load rebound among those animals undergoing STI-HAART early after infection (Lori, F. et al. Control of SIV rebound through structured treatment interruptions during early infection. Science 290, 1591-1593. (2000)), those initiating STI-HAART during AIDS, and the same animals treated with STI-HAART plus DermaVir$_{SHIV}$ revealed an interesting pattern. The rate of viral rebound during consecutive HAART interruptions, that was unchanged before the initiation of vaccine therapy, decreased sharply after vaccination, and became remarkably similar to that observed in the animals treated with STI-HAART early after infection (Fig. 14). These results suggest that DermaVir$_{SHIV}$ therapy can improve the control of virus replication during interruption of HAAR." (pg 53, lines 18-27).

Lori of record (2000) described HAART therapy used in the method above was PMPA (tenofovir, an RT inhibitor), ddI (didanosine, an RT inhibitor) and hydroxyurea (pg 1591, col. 3, lines 10-18). STI-HAART is structured treatment interruptions of HAART therapy.

The interrupted administration of PMPA, ddI and hydroxyurea followed by administration of DermaVir$_{SHIV}$ (AIDS(DermaVir)) in Fig. 14 shows decreased viral rebound as compared to interrupted administration of PMPA, ddI and hydroxyurea (AIDS(STI)).

Administering a PMPA, ddI and hydroxyurea in combination with DermaVir as described in the example is equivalent to administering an RT inhibitor and hydroxyurea followed by a gene delivery complex (Group I in the restriction sent 4-9-03) and does not correlate to administering ddI and indinavir as claimed (Group II in the restriction sent 4-9-03). In particular, the combination of PMPA, ddI and hydroxyurea is considered HAART while the combination of ddI and indinavir is not according to Celentano (cited above).

Pg 52, line 28, through pg 53, line 6, states:

> "The dynamics of viral rebound in each nnimal were also interesting. During the first therapy interruption after HAART-DermaVirSHIV treatment, two animals (#51, #56) had partially controlled viral rebound even before therapy was re-initiated ('Fig. 13a,b). Viral rebound further decreased during the next treatment interruptions. It remained undetectable in one animal (#56) after the second, and in the other animal (#51) after the third treatment interruptions. The viral load of monkey #56 had remained undetectable from the second interruption cycle until the following 90 days (Fig. 13b). Although in the third animal (#60) a virus rebound was consistently observed during treatment interruptions probably because of the onset of a drug-resistant mutant, the extent of the rebound progressively decreased (Fig. 13c)."

The specification does not compare the CD4 levels and SIV RNA levels in the test macaques in Fig. 13A-C to the CD4 levels and SIV RNA levels in control macaques receiving the same interrupted HAART therapy in the absence of DermaVir.

Rejection

The combination of administering PMPA, ddI and hydroxyurea plus $DermaVir_{SHIV}$ in the example does not correlate to administering ddI and indinavir plus $DermaVir_{SHIV}$ as claimed because the combination of PMPA, ddI and hydroxyurea is considered HAART while the combination of ddI and indinavir is not according to Celentano (cited above). It is noted that administering an RT inhibitor and hydroxyurea followed by a gene delivery complex was found to be patentably distinct from administering an RT inhibitor and a protease inhibitor followed by a gene delivery complex (Groups I and II, respectively, in the restriction sent 4-9-03). Thus, administering highly active antiretroviral therapy (HAART) followed by $DermaVir_{SHIV}$ appears to be essential to obtain the result observed in Fig. 14 because the combination of ddI and indinavir is not considered highly active. Furthermore, PMPA and ddI (both RT inhibitors) have

different structures that both inhibit reverse transcriptase using two different mechanisms of action (see DeClercq, Current Medicinal Chemistry, 2001, Vol. 8, pg 1543-1572; ¶ bridging pg 1553-1554; nucleotide vs. nucleoside analogues; "PMPA only needs two phosphorylation steps to be converted to the active metabolite")). When combined with hydroxyurea (of a different drug class altogether), the virus is being attacked by three different means. Accordingly, it appears that HAART is essential to decrease viral load long enough to allow the immune system to recognize retroviral proteins encoded by DermaVir as suggested by applicants on pg 20, lines 27-31. Applicants have not provided any correlative evidence that ddI (an RT inhibitor) and indinavir (a protease inhibitor) alone decrease viral load to the same degree as HAART or that that ddI and indinavir can decrease viral load long enough to allow adequate production of cells that recognize retroviral proteins encoded by DermaVir that are capable of treating retroviral infection. Given the unpredictability in the art regarding the parameters required to obtain a therapeutic effect using DNA and the unpredictability of treating retroviral infection, HAART is essential to the invention and does not correlate to using ddI and indinavir as claimed.

Accordingly, it would have required one of skill undue experimentation to obtain an additional decrease in viral load using DermaVir in combination with ddI and indinavir as compared to using ddI and indinavir alone. It would have required one of skill undue experimentation to determine the combinations of antiretroviral drugs capable of decreasing viral load to the same degree as PMPA, ddI, and hydroxyurea or that

decrease viral long enough to allow the immune system to recognize retroviral proteins encoded by DermaVir.

Therefore, the specification fails to enable those of skill to use ddI and indinavir followed by DermaVir such that a therapeutic immune response against the retroviral proteins encoded by DermaVir is obtained.

The teachings in the specification are also inadequate because the specification does not teach the structure of the DNA used, the dosage or route of administration that resulted in the immune response observed in Fig. 14. While the specification provides generic teachings throughout the specification about the DNA encompassed by the invention, the dosage and route of administration, the field of gene therapy and the field of treating retroviral infection were unpredictable. As such, it would require one of skill in the art undue experimentation to overcome the unpredictability and determine the combination of structural DNA elements, route of administration and dosage required to obtain a therapeutic or prophylactic effect against retroviral infection using DNA. The amount of experimentation is undue because of the numerous attempts to obtain a therapeutic effect against retroviral infection known in the art at the time of filing that failed taken with the teachings in Fig. 14 and lack of guidance about what DNA, route of administration and dosage were used to decrease viral load.

It is noted that the results in Fig. 13A-C fail to indicate DermaVir caused statistically significant increase in CD4 cells or decrease in viral rebound because the

experiments did not include controls - animals that received antiretroviral drug therapy without the gene delivery complex.

Upon addressing the enablement issues above, the claims are not enabled for administering antiretroviral drugs as broadly claimed. Claim 28 encompasses administering continuous HAART followed by DermaVir$_{SHIV}$; however, the example is limited to interrupted HAART. The specification does not correlate decreasing viral rebound obtained by interrupting HAART followed by DermaVir$_{SHIV}$ with expected results obtained by administering continuous HAART plus DermaVir$_{SHIV}$ (i.e. the virus does not rebound during continuous HAART). In fact, it appears that continuous HAART would not allow the immune system to regenerate long enough to recognize retroviral proteins encoded by DermaVir. Therefore, the mode of drug delivery in the example does not correlate to any mode of delivery as broadly encompassed by claim 28.

Upon addressing the enablement issues above, the specification does not enable administering any DNA encoding any immunogenic retroviral proteins as claimed. The claims encompass delivering any gene complex comprising DNA encoding any immunogenic retroviral protein; however, the example is limited to DermaVir$_{SHIV}$. The specification states:

> "DermaVir$_{SHIV}$ is a glucose-water solution containing a plasmid DNA as an active ingredient and polyethylenimine-mannose (PEIm) as an adjuvant (See Example 12). One therapeutic application contained 0.1 mg DNA capable of expressing all but the integrase protein of the Simian-Human Immunodeficiency Virus (SHIV). DermaVir$_{SHIV}$ was formulated to transduce Langerhans cells located in the epidermis and it was applied on the surface of the skin of the

> animals. We have shown that these Langerhans cells are triggered to migrate to the lymph nodes, mature to dendritic cells and present SHIV antigens to naïve T cells. After SHIV-specific activation of naïve T cells in the lymph nodes, $DermaVir_{SHIV}$ initiated potent SIV-specific T cell-mediated immune responses in uninfected monkeys (See Example 12)" (pg 52, lines 1-9).

The specification does not correlate the results obtained with $DermaVir_{SHIV}$, which expresses all retroviral proteins except integrase, to any DNA encoding any immunogenic retroviral protein as broadly claimed, specifically DNA encoding one immunogenic retroviral proteins, such as gp120. Numerous references are available that indicate gp120, for example, is inadequate to induce a therapeutic effect against retroviral infection. Given the unpredictability in the art of gene therapy and the art of treating retroviral infection, the expression of all retroviral proteins in DermaVir is essential to induce the proper immune response and decrease viral rebound. (see pg 52, lines 1-9).

Upon addressing the enablement issues above, the specification does not enable administering DNA encoding immunogenic retroviral proteins using any means of delivery as broadly claimed. The mode of delivery described in the specification is limited to dermal administration. Given the unpredictability in the art of gene therapy and the art of treating retroviral infection, dermal administration is essential to target adequate numbers of antigen presenting cells, present adequate amounts of retroviral proteins to cells of the immune system such that the proper immune response and decrease viral rebound occur.

In conclusion, the examples in the specification are not coextensive with ddI and indinavir and include numerous narrower embodiments than the claimed invention, i.e.

the mode of delivery of the drugs, the gene complex being delivered and the mode of delivery of the gene complex. Decreasing viral rebound after interrupting two RT inhibitors and hydroxyurea cannot even be extrapolated to administration of ddI and indinavir because the combination of drugs in the example are so structurally and functionally different and essential to obtaining an additional decrease in viral rebound as compared to using antiretroviral drugs alone.

In the paragraph bridging pg 19-10 of the response filed 12-23-05, applicants discuss the invention but do not address the basis of the rejection – that the combination of ddI, PMPA and hydroxyurea followed by DermaVir used to decrease viral rebound as in Fig. 14 is essential to obtain a decrease in viral rebound, and that ddI, PMPA and hydroxyurea followed by DermaVir does not correlate to using ddI and indinavir followed by DermaVir as claimed because the drugs have different mechanisms of action, are of different classes and would act differently in combination with DermaVir. Applicants mention Fig. 13A-C but fail to indicate the experiment used proper controls - animals that received antiretroviral therapy without receiving the gene complex. Applicants' have not taught how Fig. 13A-C shows that the gene delivery complex caused a therapeutic immune response against retroviral proteins. Applicants mention pg 20, lines 27-31, without correlating the teachings to the claims. Pg 20, lines 27-31, merely discusses treating active infections by suppressing virus replication and using the vaccine (DermaVir?) to strengthen the immune system's ability to recognize

"new variants of the virus, thereby providing a means of controlling viral replication in individuals that have already been infected." Pg 20, lines 27-31, does not discuss the combination of drugs to use with DermaVir capable of obtaining an additional decreased in viral load as compared to using drugs alone or correlate the combination of ddI, PMPA and hydroxyurea with the combination of ddI and indinavir.

Applicants point to pg 24, lines 24-25, which merely states the "following examples are presented for the purpose of illustrating the practice of the invention. They do not limit the invention, or the claims which follow." Pg 24, lines 24-25, does not address the unpredictability in the art of gene therapy or retroviral therapy or correlate using ddI and indinavir with using ddI, PMPA and hydroxyurea in combination of DermaVir. The examiner has provided scientific reasoning and evidence why the specification does not enable one of skill to use ddI and indinavir in combination with DermaVir to obtain an additional decrease in viral rebound as observed by applicants when using ddI, PMPA and hydroxyurea in combination with DermaVir in Fig. 14.

Applicants point to pg 21, line 17-25, which states:

> "Current antiretroviral drug regimens typically rely on one or more reverse transcriptase inhibitors, protease inhibitors, and a variety of other drugs including immune system treatments and a variety of unique agents, and may include 2-4 (or more) compounds, administered together. Highly active antiretroviral therapy a name commonly used in the field of HIV infection to mean combinations of three or more drugs, including at least one reverse transcriptase inhibitor and one protease inhibitor, or any combination of the drugs described below might be used according to the present invention for treatment of HIV infection. Hydroxyurea-containing combinations are preferred."

Pg 21, lines 17-25, generically discusses drug regimens without teaching which drugs are "highly active" or used in HAART (highly active antiretroviral therapy). Pg 21,

lines 17-25, does not address the unpredictability in the art of gene therapy or retroviral therapy or correlate using ddI and indinavir with using ddI, PMPA and hydroxyurea in combination of DermaVir. Pg 21, lines 17-25, states "any combination of the drugs below MIGHT be used according to the present invention" (emphasis added); however, the examiner has provided scientific reasoning and evidence why the specification does not enable one of skill to use any combination of drugs disclosed, specifically ddI and indinavir, in combination with DermaVir to obtain an additional decrease in viral rebound other than ddI, PMPA and hydroxyurea as described in Fig. 14. Pg 21, lines 17-25, does not correlate the use of two RT inhibitors having two different mechanisms of action with hydroxyurea as described in Fig. 14 with the use of one RT and one protease inhibitor alone as claimed. Nor does pg 21, lines 17-25, teach ddI and indinavir alone are adequate to decrease viral load long enough to allow the immune system to recognize retroviral proteins encoded by DermaVir as suggested by applicants on pg 20, lines 27-31.

Applicants point to pg 43, first paragraph, which describes the T-cell immune response in primates after transcutaneous PEIm/DNA immunization. Applicants' argument is not persuasive because pg 43 does not disclose the CTL response observed after DNA immunization was therapeutic, because the SHIV used on pg 43 encoded the envelope gene of HIV (gp160), because Weber (cited above) taught plasmid DNA encoding gp160 does not have a therapeutic effect in humans, and because inducing a CTL response in macaques using DNA encoding HIV gp160 does

not correlate to expected results in humans. Furthermore, the claims are not limited to transcutaneous immunization or immunizing non-human primates.

Applicants point to pg 49, lines 22-23, and argue results obtained in monkeys correlates to results obtained in humans. Applicants' argument is not persuasive. Pg 49, lines 22-23, merely correlates STI-HAART in monkeys and humans. Pg 49, lines 22-23, does not correlate using DermaVir in monkeys and humans or using STI-HAART in combination with DermaVir in monkeys and humans. Pg 49, lines 22-23, does not overcome the teachings of Weber (cited above) who taught plasmid DNA encoding gp160 does not have a therapeutic effect in humans, and that inducing a CTL response in macaques using DNA encoding HIV gp160 does not correlate to expected results in humans.

Likewise, pg 50, lines 18-19, pg 51, lines 4-7 and 9-11, cited by applicants correlate STI-HAART in monkeys and humans without addressing the use of DNA encoding gp160 in monkeys and humans or addressing the unpredictability of using DNA encoding HIV gp160 in humans described by Weber (cited above).

Applicants cite pg 53, line 7-17, which states irregular response of CD4 counts during interrupted STI-HAART treatment in combination with DermaVir in macaques correlates with results found in humans. Applicants' argument is not persuasive because pg 53, lines 7-17, does provide any indication that interrupted STI-HAART in combination with DermaVir did not cause a statistically significant increase in CD4 counts and because the results were not compared to the proper control (interrupted STI-HAART therapy alone).

Applicants argue the scope of the pending claims is equivalent to claims issued in the parent case 09/153198. Applicants' argument is not persuasive. The claims issued in '198 are merely toward a composition comprising a gene delivery complex and do not require using the gene delivery complex in combination with antiviral drug therapy to treat retroviral infection as claimed.

Applicants argue the specification provides adequate guidance indicating the DNA contributed to a therapeutic effect because the application includes in vivo results of monkeys treated with drug therapy until the drug therapy began to fail, then the DermaVir was added "and CTL responses were resurrected in deathly ill animals so that they had enhanced control of viremia and lived longer" (pg 14 of response filed 12-23-05, third paragraph). Applicants' argument is not persuasive. Fig. 14 is the only possible example described in the specification to which applicants may be referring; however, the results in Fig. 14 were obtained using ddI, PMPA and hydroxyurea followed by DermaVir which does not correlate to using ddI and indinavir as claimed followed by DermaVir for reasons cited above in the basis of the rejection, and the specification does not teach the retroviral proteins encoded by the DNA in DermaVir. Given the unpredictability in the art taken with the lack of teachings in the specification and the lack of correlation between ddI, PMPA and hydroxyurea and ddI and indinavir as claimed, it would have required those of skill undue experimentation to treat retroviral infection using ddI and indinavir followed by DNA encoding at least one retroviral protein as claimed.

Applicants argue the results in the specification included proper controls. Applicants cite pg 50, lines 3-5, 12-22, and pg 51, lines 17-21. Applicants' arguments are not persuasive. Nowhere does the specification disclose the CD4 counts and SIV RNA levels of macaques receiving interrupted HAART alone so that one of skill could determine whether the macaques receiving interrupted HAART followed by DermaVir in the paragraph bridging pg 52-53 (Fig. 13A-C) had a statistically significant increase in CD4 or decrease in SIV RNA caused by DermaVir. Applicants discuss the various macaques that received HAART and STI-HAART in the absence of DermaVir that died. Applicants fail to discuss where the specification teaches the CD4 levels or SIV RNA levels for macaques receiving interrupted HAART in the absence of DermaVir so that one of skill could evaluate whether the results in the paragraph bridging pg 52-53 (Fig. 13A-C) were statistically significant. Such controls are essential to determine whether DermaVir caused an additional increase in CD4 levels or an additional decrease in SIV RNA levels.

Applicants argue the experiments use drugs known in the art at the time of filing as being effective in treating HIV, and listed by name in the application. Applicants' argument is not persuasive for reasons above. To reiterate:

> Pg 21, lines 17-25, generically discusses drug regimens without teaching which drugs are "highly active" or used in HAART (highly active antiretroviral therapy). Pg 21, lines 17-25, does not address the unpredictability in the art of gene therapy or retroviral therapy or correlate using ddI and indinavir with using ddI, PMPA and hydroxyurea in combination of DermaVir. Pg 21, lines 17-25, states "any combination of the drugs below MIGHT be used according to the present invention" (emphasis added); however, the examiner has provided scientific reasoning and evidence why the specification does not enable one of skill to use any combination of drugs disclosed, specifically ddI and indinavir, in combination with DermaVir to obtain an additional decrease in viral rebound other than ddI,

PMPA and hydroxyurea as described in Fig. 14. Pg 21, lines 17-25, does not correlate the use of two RT inhibitors having two different mechanisms of action with hydroxyurea as described in Fig. 14 with the use of one RT and one protease inhibitor alone as claimed. Nor does pg 21, lines 17-25, teach ddI and indinavir alone are adequate to decrease viral load long enough to allow the immune system to recognize retroviral proteins encoded by DermaVir as suggested by applicants on pg 20, lines 27-31.

Applicants' arguments do not address the fact that claims encompass numerous means of delivering the antiretroviral therapy, while the examples are limited to interrupted HAART therapy, followed by administering the gene delivery complex.

Applicants' arguments do not address the fact that the claims encompass numerous gene delivery complexes encoding at least one immunogenic retroviral protein while the teachings in the specification are limited to DermaVir

The prior art

The effective filing date for the concept of delivering DNA in combination with mannosylated PEI as claimed goes back to 9-15-98, parent application 09/153198. Provisional application 60/058933 filed 9-15-97, does not teach delivering DNA in combination with mannosylated PEI as claimed.

The effective filing date for the concept of delivery DNA in combination with mannosylated PEI after antiretroviral therapy is 5-23-01, the filing date of the instant application. Neither parent application 09/153198 (filed 9-15-98) or provisional application 60/058933 (filed 9-15-97) teach delivering DNA in combination with mannosylated PEI after antiretroviral therapy.

MacGregor (Program and Abstracts of the 6th Conference on retroviruses and opportunistic infections, Chicago, 1999, pg 133, Abstract No: 347) administered two DNA encoding HIV-1 genes env/rev and gag/pol genes to HIV-positive subjects intramuscularly whose viral production is suppressed by HAART. HAART does not correlate to administering ddI and indinavir as claimed. MacGregor did not teach administering the DNA using mannosylated polyethylenimine as claimed.

Boussif (PNAS, Aug. 1995, Vol. 92. pg 7292-7301) of record, administered DNA encoding the marker protein luciferase to the brain of mice using PEI.

Zanta (Bioconjugate Chem. 1997. Vol. 8. pg 839-844) of record, administered DNA encoding a marker protein to cells *in vitro* using PEI-galactose or PEI glucose.

Behr (US Patent 6,013,240) of record, administered DNA encoding a marker protein to cells *in vitro* using PEI.

The use of mannosylated PEI to deliver DNA in vivo as claimed was not described until the proceedings of the 3rd European conference on gene therapy of cancer, held from Sept. 11-13, 1997 at the University of Berlin, as supported by Diebold of record (Advances in Experimental Med. and Biol., Oct. 1998, Vol. 451, pages 449-455) (see IDS filed 3-11-04). The preface of Advances in Experimental Med. and Biol., Oct. 1998, Vol. 451 (page v and vi) states that Vol. 451 contains the proceedings of the 3rd European conference on gene therapy of cancer. At the conference Diebold taught a complex comprising i) mannosylated PEI (PEI-man), and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter used to transfect dendritic cells via the mannose receptor (pg 452, line 10; pg 453, line 13-18).

While Diebold described using a complex comprising PEI-man and DNA encoding an immunogenic protein at least a year and two days prior to the filing date of parent application 09/153198 (Sept. 15, 1998), the conference was in Germany. 102(a) and (b) require that the information known in this country or published in this country or a foreign country prior. It does not appear that the information disclosed by Diebold was known in this country or published in any country until the publication of the article in Advances in Experimental Med. and Biol. in Oct. 1998.

Therefore, the information disclosed by Diebold at the conference is not available under 102(a) or (b) because it was not known or published in this country prior to 9-15-98. Ergo the information disclosed by Diebold at the conference is not available under 103.

The information disclosed by Diebold of record (Advances in Experimental Med. and Biol., Oct. 1998, Vol. 451, pages 449-455) is not available under 102(a) or (b) because it was not available at the effective time of filing – September 15, 1998. Ergo, the information disclosed by Diebold of record (Advances in Experimental Med. and Biol., Oct. 1998, Vol. 451, pages 449-455) is not available under 103.

Thus, claims 28-30 remain free of the prior art as they relate to administering antiretroviral drug therapy comprising ddI (an RT inhibitor) and indinavir (a protease inhibitor) until viral replication is suppressed, and then administering a DNA complex comprising a) DNA encoding at least one immunogenic retroviral protein operably linked with a promoter; and b) mannosylated polyethylenimine. The prior art did not teach or

suggest administering ddI and Indinavir until viral replication is effectively suppressed, and then administering a gene delivery complex comprising DNA encoding an immunogenic retroviral protein and mannosylated polyethylenimine as claimed.

Double Patenting

Claims 28-30 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,420,176 (US Patent Application 09/153,198) in view of the disclosure of 6,420,176 for reasons of record.

The claims of '176 are directed toward a gene delivery complex comprising DNA encoding an immunogenic protein operably linked to a promoter and monosylated polyethylenimine. The claims of '176 do not require administration of ddI and indinavir followed by administration of the gene delivery complex as required in the instant claims. MPEP 804 states the specification may be used as a dictionary to learn the meaning of a term in the patent claim. In this case, one of skill would look to the specification to determine the asserted utility of the product. The disclosure taught administering the gene delivery complex after suppressing viral replication using antiretroviral drug therapy (col. 12, lines 11-51, see especially lines 20-27). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the gene delivery complex in combination with drug therapy as claimed.

Applicants discuss the terminal disclaimer in parent application '176; however, the terminal disclaimer in '176 does not obviate the instant rejection. Applicants must file a terminal disclaimer in the instant application over the patent term of '176.

Applicants argue the present application contains "significant additional disclosure relating to drug treatments that can be used in combination with the vaccine, and experiments conducted subsequent to the filing of the parent patent, which yielded a new method of treating existing infection. The division of the parent patent is incapable of yielding claims that overlap with the claims that are currently being considered, because the divisional application does not contain disclosure that the Examiner will consider enabling disclosure relating to the use of the claimed method of using drug treatments in conjunction with the claimed vaccine." Applicants' argument is not persuasive because parent application '176 disclosed administering the gene delivery complex after antiretroviral drug treatment.

The rejection of claims 28-31 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 10/081922 has been withdrawn in view of the terminal disclaimer filed over 10/081922 filed 12-23-05.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER